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Quantitative Assessment of Lives Lost Due to Delay in the Regulation of Occupational Exposure to Benzene

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Benzene exposure can cause leukemia, aplastic anemia, and possibly lymphoma. In 1978, on the basis of strong but incomplete data then available on the risk of benzene-induced leukemia, the U.S. Occupational Safety and Health Administration (OSHA) reduced the permissible occupational exposure standard for benzene from 10 ppm to 1 ppm. Shortly thereafter, the Fifth Circuit Court of Appeals stayed this ruling, and in 1980, the Supreme Court overturned the regulation, citing insufficient evidence of benefit. Thus, from 1978 until the standard was again lowered to 1 ppm in 1987, American workers were exposed to benzene at levels in excess of 1 ppm. An estimated 9600 were exposed to levels between 1 and 10 ppm, and an additional 370 were exposed at levels above 10 ppm.

To assess the risk resulting from this delay in regulation, we have conducted an epidemiologic risk analysis. We merged data on numbers of persons (238,000) exposed to benzene in seven occupational categories with dose-response data from three epidemiologic studies. The range of risk in these studies indicates that 44 to 152 excess leukemia deaths will ultimately result from exposure to benzene at 10 ppm over a working lifetime (45 years) and that lower or briefer exposures will result in proportionately fewer deaths. On this basis, we calculated that between 30 and 490 excess leukemia deaths will ultimately result from occupational exposures to benzene greater than 1 ppm that occurred between 1978 and 1987. Deaths from aplastic anemia and lymphoma will likely add to this toll. These data confirm the risk of regulatory delay. They suggest that the courts, in reviewing public health regulations, must beware of facile cost-benefit arguments and be willing to accept strong evidence of health risk even when such evidence is incomplete.

Introduction

Clinical, epidemiologic, and toxicologic data indicate that occupational exposure to benzene can cause leukemia. The etiologic association was first suggested by case reports originiating more than 50 years ago (*1–5*). Those observations were corroborated by epidemiologic studies among shoe workers (*6*), chemical workers, and rubber workers (*7–11*). Recently, benzene has been found to be carcinogenic in animal bioassays (*12–16*). Benzene was formally declared a human carcinogen by the National Institute for Occupational Safety and Health (NIOSH) in 1976 (*17*), by the U.S. Environmental Protection Agency (EPA) in 1979 (*18*), and by the International Agency for Research on Cancer (IARC) in 1982 (*19*).

The regulatory history of benzene has been turbulent. Particular controversy has surrounded efforts to regulate occupational exposure to benzene at relatively low levels, because until recently only qualitative information was available on the risk of leukemia at low levels of exposure to benzene. In 1978 the Occupational Safety and Health Administration (OSHA) promulgated an occupational exposure standard reducing permissible workers' exposures by 10-fold, from the previously acceptable 8 hr time-weighted average (TWA_8) of 10 ppm to 1 ppm (*20*). This action was based on information from case reports and two epidemiologic studies (*21*). Both of those studies demonstrated statistically significant excess mortality from leukemia in workers exposed to benzene, but neither presented sufficient data on exposure to permit examination of quantitative dose-response relationships (*8,9*).

On July 2, 1980, in a decision of profound importance for governmental risk assessment, the U.S. Supreme Court invalidated the OSHA benzene standard of 1 ppm (*22*). The Court stated that OSHA had failed to provide substantial evidence of the need for regulation, in that it had not quantified a "significant risk of material health impairment" at the previous level of 10 ppm and had not established that a new standard would achieve "a substantial reduction in significant risk." As a result of this decision, workers in the United States were allowed to be exposed at levels up to 10 ppm. That situation per-

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sisted until December 1987 when, on the basis of new, highly quantitative epidemiologic and toxicologic data, OSHA reimposed a 1-ppm standard (*23*).

We have undertaken a quantitative assessment of the number of excess deaths from leukemia that ultimately will result from this 10-year delay in regulation. This analysis merges information developed by OSHA on numbers of workers exposed to benzene at various concentrations in seven industrial categories with quantitative data from epidemiologic studies on risk of benzene-induced leukemia. This analysis provides a basis for reconsideration of the premises underlying the 1980 Supreme Court decision on benzene.

Methods

Populations Exposed to Benzene

In its final benzene rule, OSHA provided estimates of the numbers of workers exposed to various concentrations of benzene in the U.S. in seven different occupational categories (*23*). Overall in 1987, 238,000 workers were occupationally exposed to benzene; approximately 10,000 wokers were exposed to time-weighted concentrations in excess of the 1-ppm standard promulgated by OSHA in 1978 (Table 1). Earlier estimates by OSHA had suggested a greater population exposure; the proposed rule (*24*) had indicated that 274,000 were exposed, 27,500 to concentrations in excess of 1 ppm.

Epidemiologic Risk Assessments

Between 1982 and 1988, at least seven quantitative risk assessments were published evaluating the risk of leukemia in persons exposed to benzene. IARC (*19*) estimated that 140 to 170 excess leukemia deaths would occur per 1000 workers exposed to benzene for a 45-year working lifetime at levels of 10 to 100 ppm (*10*) and that 72 excess deaths per 1000 workers would occur from exposures of the same duration at levels between 1 and 30 ppm (*9*). Using geometric means to estimate average exposures, these data suggest that 44 to 132 excess deaths from leukemia will occur per 1000 workers exposed at 10 ppm benzene for a 45-year working lifetime.

OSHA staff members published a risk assessment which estimated that 44 to 152 excess leukemia deaths will occur per 1000 workers for the same exposure conditions (*25*). Another risk assessment commissioned by OSHA for their review of the standard in 1984 indicated the best estimate of risk to be 95 excess leukemia deaths per 1000 workers at benzene exposures of 10 ppm for a working lifetime (*23*). This estimate was based on an analysis of data from three exposed populations. A 1979 EPA assessment, although methodologically imprecise, was in approximate agreement with the above analyses (*18*).

Those risk assessments used slightly different methodologies and considered different models for the dose- and time-course of benzene-related leukemias. Nevertheless, the results were in remarkable agreement. The results of all of the analyses fall within the range of the OSHA estimate of 44 to 152 excess leukemia deaths per 1000 workers exposed to benzene for 45 years at concentrations of 10 ppm. All of the above analyses were based upon estimates of group exposure.

More recently, research has been published by Rinsky et al. (*11*) on the risk of leukemia related to the benzene exposures of individual subjects. The results indicate, that the above assessments based on group exposure may actually underestimate the risk of benzene-induced leukemia. Table 2 shows observed and expected deaths from leukemia according to cumulative individual exposure. A weighted least-squares regression line through an SMR of 100 at zero exposure yields the relationship:

$$\mathrm{SMR} = 100 + 0.035 \times \mathrm{ppm}.$$

The standard error on the coefficient of cumulative exposure in this equation is 0.024 to 0.045.

Rinsky et al. performed a matched case-control analysis of their data using conditional logistic regression. The odds ratio (OR) for leukemia in relation to cumulative benzene exposure was determined to be

$$\mathrm{OR} = \exp(0.0126 \times \text{ppm-years}).$$

Because of the exponential relationship, risks predicted by this model are extremely high for cumulative exposures in excess of 300 ppm-years.

We have estimated the excess leukemia mortality from this exposure-response relationship using a life-table analysis, with the risk lagged by 5 years. The results for a 45-year exposure, beginning at age 25, suggest that 71 to 132 of 1000 workers initially exposed to benzene at 10 ppm will die of benzene-related leukemia. A dose-response relationship determined from a case-control analysis of the data from this study suggests an even higher mortality.

Table 1. Number of workers exposed to benzene and current exposure levels by industry divisions (*23*).

Industry	Exposure category by 8-hr time-weighted average benzene concentrations, ppm						Total number of workers
	0.0–0.1	0.11–0.5	0.51–1.0	1.1–5.0	5.1–10	10+	
Petrochemical plants	—	3,208	—	989	103	0	4,300
Petroleum refineries	30,715	12,410	2,187	1,807	238	190	47,547
Coke and coal chemicals	00	372	261	260	42	12	947
Tire manufacturers	34,710	24,375	4,095	1,820	—	—	65,000
Bulk terminals	15,661	8,887	1,436	1,003	81	27	27,095
Bulk plants	26,197	14,866	2,402	1,677	136	45	45,323
Transportation via tank truck	32,558	10,996	2,523	1,380	48	95	47,600
Totals	139,841	75,113	12,904	8,936	647	370	237,812

An analysis by Crump and Allen (*26*), which used the same data base as that used by Rinsky et al. (*11*), and which employed a relative risk model, found an excess risk of death from leukemia of 72 per 1000 workers exposed to 10 ppm for a 45-year working lifetime.

An additional analysis of the data of Rinsky et al. was undertaken by Austin et al. (*27*) using the risk assessment methodology proposed by Enterline et al. (*28*). This analysis estimated that 125 excess leukemia deaths could result per 1000 workers exposed for a 45-year working lifetime to 10 ppm benzene. A further analysis by Austin et al., based on the Dow Chemical Company cohort (*9*), found that 69 excess leukemia deaths would result per 1000 workers exposed over a 45-year working lifetime to 10 ppm benzene.

Results

From these risk assessments, we have estimated the number of lives of American workers that ultimately will be lost because of exposure to unnecessarily high concentrations of benzene between 1978 and 1987. We used data on the sizes of the exposed population from Table 1. We used the estimate from OSHA (*25*) that 44 to 152 excess leukemia deaths per 1000 workers will result from 45 years of occupational exposure to benzene at 10 ppm and that shorter and lower exposures will result in proportionally fewer deaths (i.e., that risk is linearly related to cumulative exposure). We calculate, on the basis of those estimates, that 30 to 105 premature leukemia deaths will eventually be caused by benzene exposures resulting from the delay in implementing a 1-ppm standard between February 1978 and September 1987. In addition to the leukemia deaths, deaths from aplastic anemia and lymphomas will likely add to this toll. If, on the other hand, the earlier population exposure estimates of OSHA (*24*) are used, the excess leukemia death toll will range from 140 to 490. If one uses the dose-response relationship of Rinsky et al. and the population estimates of Table 1, depending on assumptions made about exposures prior to 1978, the number of excess deaths will range from 80 to 1000 or more.

The above mortality estimates were calculated using the relationship

$$\text{Total deaths} = P_i \times (E_i - E_r) \times R \times (9.6/45)$$

Here P_i is the population (in thousands) in one of the three highest exposure categories of Table 1; E_i is the category average benzene exposure in ppm; E_r is the residual exposure under a 1-ppm standard; R is the risk for a 45-year exposure to 1 ppm, either 4.4/1000 or 15.2/1000 and (9.6/45) is the fraction of 45 years that the 1-ppm standard was delayed. The average exposures used in these calculations were geometric means, 2.2 ppm and 7.1 ppm for the exposure ranges 1.1 to 5.0 ppm and 5.1 to 10 ppm, respectively, and 30 ppm for the 10+ ppm category. We assumed that the residual average exposure for individuals in these categories under a 1-ppm PEL standard would be 0.3 ppm. Typically, average exposures cannot exceed one-third of the PEL if compliance with the standard is to be maintained.

It is not certain which of these estimates is correct. The lowest is very likely an underestimate, because the population estimated in the OSHA final rule were derived principally from exposure concentrations measured after 1985; higher exposure values would likely have existed in earlier years. The highest estimate may be an overestimate, because of uncertainties in the dose-response relationship (stemming from the small of cases), particularly

Discussion

The data presented in this analysis show that a court-imposed 10-year delay in the regulation of occupational exposure to benzene resulted in substantial unnecessary excess mortality from leukemia (*29*). The U.S. Supreme Court, in its 1980 ruling, established a new criterion that must henceforth be met by OSHA in the promulgation of workplace health standards, namely, that a "significant" risk must be shown to exist under present conditions and that this risk will be significantly reduced by a new standard. This approach to regulation breaks precedent with

Table 2. Observed and expected deaths from leukemia in rubber workers exposed to benzene between 1940 and 1965 by cumulative exposure and years of latency (*11*).

	Exposure, ppm-year				
Latency, years	0.001–40	40–200	200–400	>400	Totals[a]
<5	2/0.10	0/0.02	—	—	2/0.12
5–10	0/0.16	0/0.05	0/0.01	—	0/0.22
10–15	0/0.22	1/0.07	1/0.02	0/0.00	2/0.31
15–20	0/0.27	1/0.09	1/0.03	2/0.01	3/0.39
20–25	0/0.32	0/0.10	0/0.03	1/0.01	1/0.46
25–30	0/0.37	0/0.12	0/0.04	0/0.01	0/0.54
>30	0/0.40	0/0.16	1/0.04	0/0.01	1/0.62
Totals[a]	2/1.83	2/0.62	2/0.17	3/0.04	9/2.66
Standardized mortality ratio	109	322	1,186	6,637	337
Confidence interval	12–394	36–1,165	133–4,285	1,334–19,393	154–641

[a]The numbers of expected deaths have been rounded.

long-standing tradition in public health. The tradition urges in the interest of disease prevention that public health regulations be set early, even on the basis of incomplete evidence. That approach embodies a conscious decision to err on the side of prevention in regulatory decision making (*30*). In the decade of regulatory inaction that followed the Supreme Court decision, additional epidemiologic and toxicologic data were developed on benzene. These data confirmed and strengthened the results of earlier analyses and documented the existence of exposure-related risk. However, as we have shown, this additional certainty was gained at a cost (*31*).

Importantly, the Supreme Court did not require that OSHA conduct a cost-benefit analysis, the basis on which the Fifth Circuit Court of Appeals initially vacated the 1978 standard. Also, the Supreme Court provided some guidance as to what might constitute a "significant health risk," suggesting that a risk of 1 death per 1000 from regular exposure might well qualify. The residual risk from a 45-year exposure to 1 ppm of benzene vapor is estimated to range from 4 to 15 deaths per 1000 exposed.

While OSHA has finally made progress in reducing what was clearly a significant risk in the case of benzene, several aspects of the Supreme Court decision continue to have disturbing ramifications. First, this decision implies that less than significant risks need not be regulated, even though such regulation might be economically feasible and of public health benefit. Second, individual risk was the only criterion listed for consideration; no mention was made of considering the number of individuals exposed to a given risk. Is a risk to 500 workers to be considered the same as a risk to 5 million workers in terms of significance? Finally, the Supreme Court decision may turn future regulatory hearings into forums arguing such nebulous questions as what risk is "significant" or what benefit is "substantial," rather than focusing on such basic scientific issues as identification of health effects, definition of dose-response relationships, and design of control measures.

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